# CONGENITAL TOXOPLASMOSIS: CLINICAL, LABORATORY, AND THERAPEUTIC CONSIDERATIONS, WITH SPECIAL REFERENCE TO SUBCLINICAL DISEASE*

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SINCE the original description of congenital toxoplasmosis by Wolf, Cowen, and Paige in 1939, chorioretinitis, hydrocephalus, and intracranial calcification have been accepted among clinicians as the "classical triad" of symptoms of intrauterine toxoplasmosis.[1, 2] Unless these findings appear in neonates, congenital toxoplasmosis is usually not considered as a cause of disease in spite of the fact that variability in clinical manifestations has been demonstrated repeatedly.[3-9] Eichenwald, after a longitudinal study of 156 congenitally infected infants summarized in 1959, stated that "congenital toxoplasmosis is a disease with an extraordinarily wide range of manifestations, so wide in fact that it must be considered in the differential diagnosis of nearly all types of obscure illness occurring during early infancy."[2] His data are summarized in Table 1 in order to illustrate clinically apparent disease.

Two types of disease were described in *symptomatic* infants. The more common had a dominant neurologic component and was seen in 69% of his patients. The other, a generalized disease, occurred in 28%. The latter was recognized earlier in life, usually within the first four weeks, because disease was more obvious, whereas months generally elapsed before the former was diagnosed. Clearly, when the dominant involvement was in the central nervous system or eye, as is

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TABLE I. SIGNS AND SYMPTOMS OCCURRING PRIOR TO DIAGNOSIS OR DURING COURSE OF ACUTE CONGENITAL TOXOPLASMOSIS

*Total—152 infants*

| *Type of disease:* | *Percentage* | | |
|---|---|---|---|
| Dominant neurologic | 69 | | |
| Generalized | 28 | | |
| *Findings:* | | *Findings:* | *Percentage* |
| Chorioretinitis | 80 | Pneumonia | 21 |
| Abnormal spinal fluid | 69 | Diarrhea | 16 |
| Anemia | 64 | Hydrocephalus | 14 |
| Splenomegaly | 56 | Rash | 13 |
| Jaundice | 54 | Hypothermia | 11 |
| Fever | 51 | Eosinophilia | 11 |
| Hepatomegaly | 47 | Abnormal bleeding | 11 |
| Lymphadenopathy | 43 | Microcephaly | 7 |
| Convulsions | 34 | Glaucoma, Optic atrophy, Microphthalmus | 1 |
| Vomiting | 32 | | |
| Intracranial calcifications | 27 | | |

Adapted from Eichenwald, H. F.: A Study of Congenital Toxoplasmosis with Particular Emphasis on Clinical Manifestations, Sequelae, and Therapy. In: *Human Toxoplasmosis,* Siim, J. C., editor. Copenhagen, Munksgaard, 1959.

usually the case, the infection lacked overt findings sufficient to suggest toxoplasmosis during the neonatal period. Hydrocephalus, microcephaly, convulsions, or intracranial calcification were rare in either infected group. They occurred in only 14, 7, 34, and 27%, respectively, of the entire infected population.[2] Chorioretinitis was common (80%) but is easily overlooked unless careful examination is performed in all sick newborns, a difficult chore! The other symptoms seen in a reasonable number of infants: e.g., anemia, splenomegaly, jaundice, fever, hepatomegaly, adenopathy, and vomiting are too nonspecific to be useful diagnostically. It is obvious from these results that congenital toxoplasmosis is easily misdiagnosed on clinical grounds, even in sick infants who have the generalized form of the disease. Those with isolated neurologic involvement may be missed entirely, as is evidenced by two infants in Eichenwald's series who were born without symptoms but developed debilitating disease of the central nervous system much later and two who remained asymptomatic throughout the four-year follow-up period. The latter two certainly had subclinical congenital toxoplasmosis, as noted.[2] Couvreur and Desmonts, who later reviewed 300 cases of congenital toxoplasmosis, reached the same conclusions about the wide spectrum of disease that accompanies this entity. They emphasized the fact that the neurological, especially the

ocular, manifestations may not appear for months or even years following congenital infection.[10] This delayed onset of disease is somewhat reminiscent of congenital syphilis.

Subclinical or very mild infections appeared to be much more frequent than the more severe, symptomatic ones in the early prospective studies of these investigators, a suggestion subsequently corroborated by them and others.[10, 11, 14] Approximately 20 to 30% of infants born with congenital toxoplasmosis have severe disease, either an acute generalized or a neurologic type (Table 1).[11, 14, 15] Another approximately 10% are born with ocular involvement without clinical evidence of disease in other organ systems.[15] The remainder, about 70%, are asymptomatic at birth and seemingly remain so for years.[11, 14] Thus, it becomes important from the standpoint of numbers to determine the true medical significance, if any, of the subclinical form of congenital toxoplasmosis. We have investigated this crucial problem in recent years and summarize our results here.

## Subjects and Methods

About five years ago we began prospective studies to gain an overview of the incidence and to determine the clinical nature of the chronic intrauterine infections, including toxoplasmosis, as they occur year in and year out in a moderately low socioeconomic urban population in the southern United States.[16] Essentially, all live births (3,000/year) at the University Hospital in Birmingham, Ala., were screened for evidence of fetal antibody production as a first step in identifying newborns who are at high risk for chronic intrauterine infection: i.e., congenital rubella and cytomegaloviral, *Toxoplasma*, and syphilitic infections.[16] The screening methods, diagnostic procedures, and clinical studies used have been detailed previously, along with some of our early results.[14, 16, 17]

For detection of congenital toxoplasmosis, two screening techniques were employed. Umbilical-cord and neonatal sera obtained for all live births over a two-and-one-half-year period from late 1967 to mid-1970 were screened for IgM elevations in order to monitor them for excess intrauterine antigenic stimulation.[17] This particular screening technique is of course nonspecific with regard to infection. Therefore, in the last one and one half years of the study the same sera were also screened for the presence of IgM-*Toxoplasma* fluorescent antibody

(IgM-FA, as described by Remington) to achieve an increased degree of specificity. [15, 17, 18] All newborns with positive tests were carefully observed in the nursery for at least two weeks. During this time ophthalmologic, spinal fluid, and radiologic examinations as well as platelet counts were performed routinely, with parental consent, whether the neonate was symptomatic or not. This was done in order to detect subtle disease in the newly born. All infants with positive screening tests were followed at monthly intervals for six months, bimonthly in the second six-month interval, and at least semiannually thereafter. IgG and IgM-FA *Toxoplasma* antibody levels were determined serially in all infants and during the first year dye-dilution antibody levels were also obtained. The diagnosis of congenital toxoplasmosis was considered to be established only if levels of IgG-FA and dye-dilution antibody remained the same or increased from birth throughout the first year of life.[2, 3, 16] General development was gauged grossly during the first two years of follow-up by means of the Gesell Developmental Schedule.[19] Between two and four years of age (average, three years) the infected infants and preselected controls were tested by the Slosson Intelligence Test for Children and Adults, the Vineland Social Maturity Scale, and a modified version of the Behaviour Record Index from Nancy Bayley's scales of infants' development in order to ascertain intelligence quotients (I.Q.) and social development.[20]

In the first five of our infected patients, identified initially by the nonspecific IgM screen, the diagnosis was finally achieved by serial antibody testing; hence treatment could not be instituted soon enough after delivery to be meaningful. In the other half, diagnosis was assumed on the basis of IgM-FA findings as described in the serology section.[18, 29, 30] These patients were treated early in the neonatal period with sulfadiazine, pyrimethamine, and folinic acid. Consequently, five of the patients were treated soon after delivery and the other five were not; this permitted a minimal assessment of the effect of treatment on long-term outcome.

## Longitudinal Clinical and Laboratory Studies

During the course of these investigations, 10 infants with proven congenital toxoplasmosis were detected out of 7,500 screened. The incidence of intrauterine toxoplasmosis as defined by this approach in our population then averaged one case per 750 deliveries for the two-

TABLE II. CLINICAL AND LABORATORY FINDINGS IN 10 NEWBORNS BORN CONSECUTIVELY WITH CONGENITAL TOXOPLASMOSIS

| | |
|---|---|
| Maternal illness ("flu) | 2 |
| Diagnosis suspected (neonate) | 1 |
| Gestational prematurity *† | 5 |
| Intrauterine growth retardation‡ | 2 |
| Hepatosplenomegaly | 1 |
| Jaundice (bilirubin < 15 mg.%) | 1 |
| Thrombocytopenia | 1 |
| Anemia | 1 |
| Chorioretinitis | 2 |
| Abnormal head size | 0 |
| Hydrocephalus | 1 |
| Microcephaly | 0 |
| Abnormal spinal fluid* | 8§ |
| Abnormal neurological | 1 |
| IgM elevations* | 9 |
| IgM *Toxoplasma* antibody* | 10 |

*Most significant new findings.
†<37 weeks gestation.
‡Lower 10th percentile (Grunewald).
§Only eight were examined.

and-one-half-year interval studied. It varied from a maximum of 1/450 in the first year to a minimum of 1/1,500 in the last year. Though impressive, these figures must be viewed as minimal, since the IgM screen used in the first year has been shown to yield false-negative results and some of the infants born with IgM-FA antibody were lost to follow-up.[17] In spite of these deficiencies, the average figure, though slightly higher, is similar to that previously reported by Eichenwald and recently by Kimball and Kean for New York City, but is somewhat less than those reported from Europe, where different screening techniques were employed.[2, 11-13]

The pertinent clinical findings seen in the newborns are summarized in Table II. Only one infant manifested signs and symptoms suggesting acute generalized toxoplasmosis. In this case severe perinatal asphyxia was followed by the development of hepatosplenomegaly and jaundice with direct reacting hyperbilirubinemia within 24 hours after delivery. Likewise, poor feeding and repeated aspiration were accompanied by the findings of diffuse transillumination of the skull, bilateral chorioretinitis, and intracranial calcification. Though treated soon after delivery, this infant died at four months of age as a result of complications of severe internal hydrocephalus, obviously incurred prenatally.

There were no overt specific signs of clinical infection in any of the other neonates. After IgM-FA antibody was demonstrated, careful

ophthalmologic examination revealed unilateral chorioretinitis in one additional neonate who was otherwise normal. Retrospective questioning of the mothers was also of no diagnostic value; two recalled having nonspecific, febrile, respiratory illnesses resembling "flu" but the others denied any sickness. Nine of the 10 infected infants would clearly have escaped detection had it not been for the laboratory screening aids being employed initially to designate newborns at high risk.

There were, however, significant abnormalties in this group of patients with so-called subclinical infections. Premature delivery occurred in 50% of the infected pregnancies, at 28 and 34 weeks in two cases and at 36 weeks in three. Therefore, the average birth weight of the infected infants (2,664 gm.) was 344 gm. less than that of the control infants (3,013 gm.). Apparently *Toxoplasma* infections in pregnant women can initiate premature labor even though disease in the infected fetus is minimal. Whether this process can occur earlier in pregnancy is an important consideration regarding the ability of *Toxoplasma* to produce abortion in women who appear to be normal. *Toxoplasma* has been suggested as a cause in such cases, especially by European workers, but their findings have been disputed.[11, 21-23] The physiologic consequences of the prematurity were of only minimal significance in our infected infants.

In spite of the lack of symptoms and of neurological findings, abnormalities of cerebrospinal fluid (CSF) indicative of central-nervous-system (CNS) disease were detected in all the infected infants in whom permission was obtained to perform lumbar puncture.[14] These abnormalities, which are depicted in Figure 1, included lymphocytosis, most often accompanied by a disportionately elevated protein level. CSF changes were present at birth and persisted for variable but prolonged intervals, ranging from two weeks to four or more months (averaging at least three months for the group). Improvement in the CSF abnormailities was very slow, even in infants in whom treatment was instituted in the first few weeks of life. Because of the variability in the degree of abnormality and the small number of infants involved, the effect of treatment on improvement in the CSF changes, unfortunately, could not be judged properly.

In a general way the initial CSF-protein level was the only real prognostic monitor with regard to development in the first year of life. A relatively severe form of disease was detected in two of the

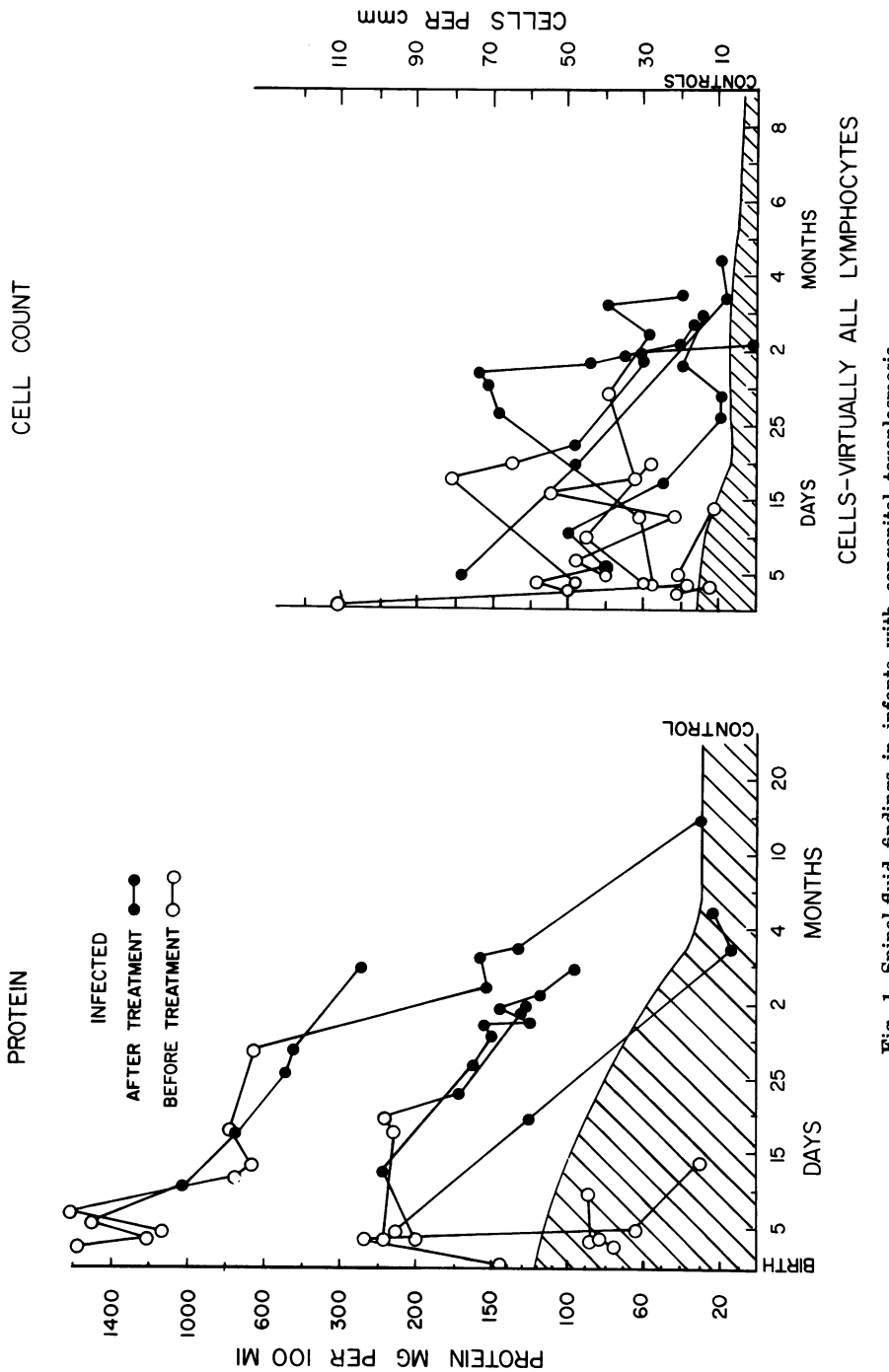


Fig. 1. Spinal-fluid findings in infants with congenital toxoplasmosis.

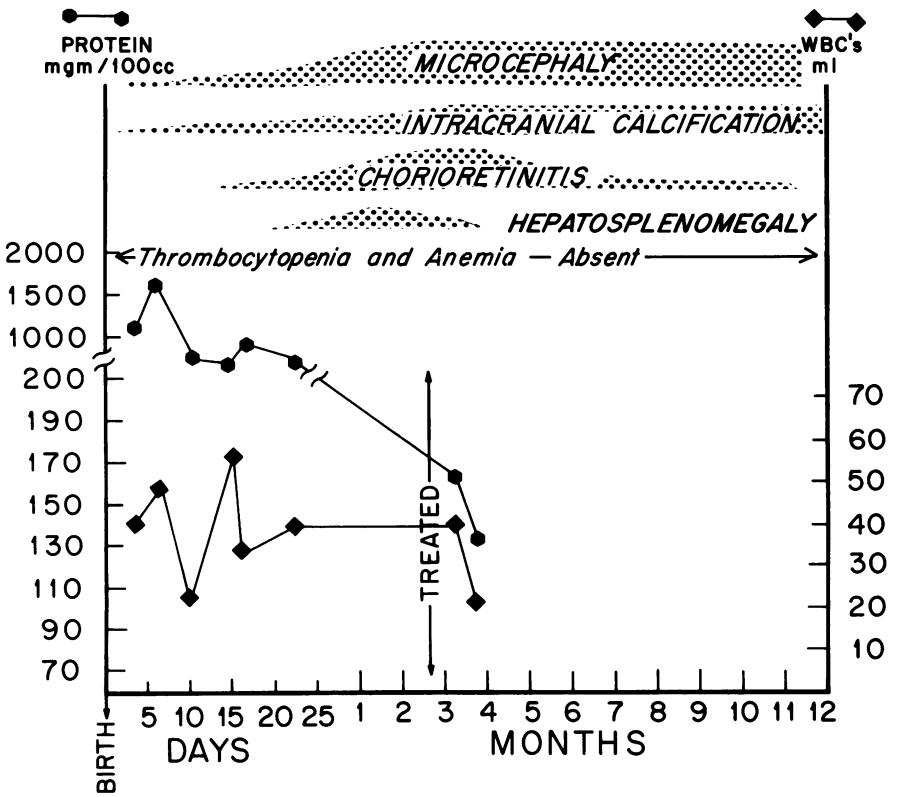


Fig. 2. Severe form of congenital toxoplasmosis. Spinal-fluid and clinical findings. Reproduced by permission from Alford, C. A., Foft, J. W., Blankenship, W. J., Cassady, G., and Benton, J. W.: Subclinical central nervous system disease of neonates: A prospective study of infants born with increased levels of IgM. *J. Pediat. 75*:1167-78, 1969.

10 infants. The findings from one of these with clinically apparent generalized disease at birth has already been described. His CSF protein was persistently elevated in the very high range from birth until his death at four months. Severe internal hydrocephalus and marked evidence of brain destruction were found at autopsy (Figure 1). The serial findings in the other infant with a relatively severe form of the neurologically dominant infection are depicted in Figure 2.[14] Although this infant was born prematurely and his growth was retarded, there were no specific signs indicative of systemic infection, neural or other, during the neonatal period. However, elevation of the level of protein in the CSF suggested severe CNS involvement from birth onward; levels ranged between 700 and 1,600 mg./100 ml. during the first month

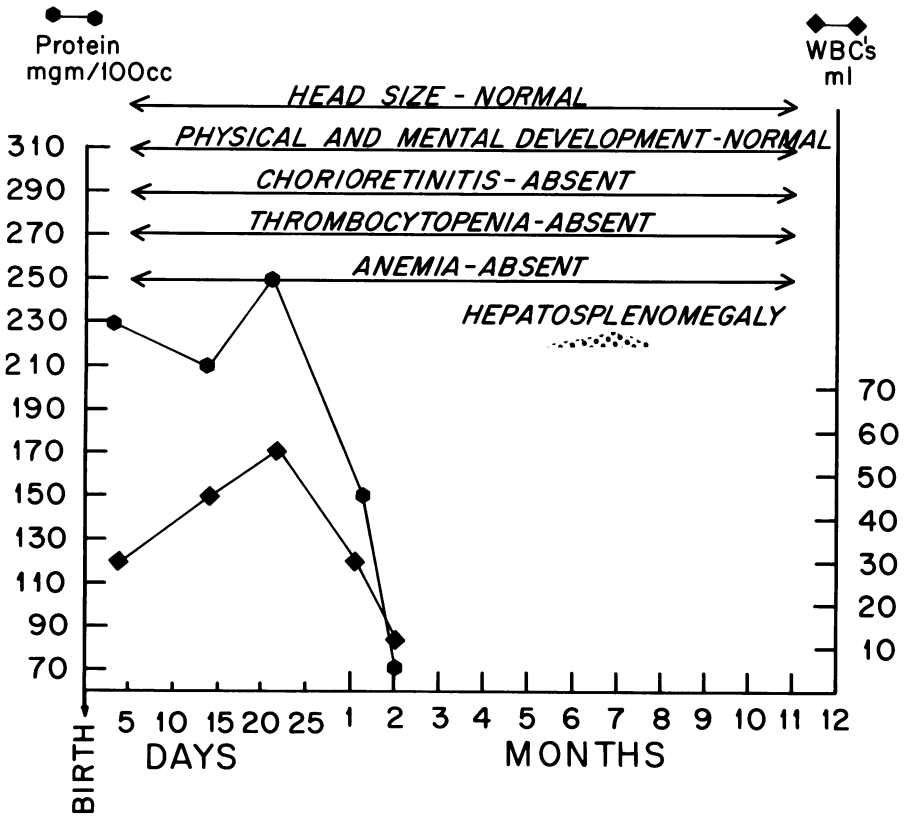


Fig. 3. Mild form of congenital toxoplasmosis. Spinal-fluid and clinical findings. Reproduced by permission from Alford, C. A., Foft, J. W., Blankenship, W. J., Cassady, G., and Benton, J. W.: Subclinical central nervous system disease of neonates: A prospective study of infants born with increased levels of IgM. *J. Pediat. 75*:1167-78, 1969.

after delivery. At approximately two and one half months retarded growth of the head, generalized intracranial calcification, chorioretinitis, and mild hepatosplenomegaly first became evident and progressed thereafter in spite of late treatment with sulfadiazine, pyrimethamine, and folinic acid. Clinical evidence of permanent and extensive brain damage has been obvious since two months; at four years the child functioned at the developmental level of two years. The chorioretinitis did, however, subside after treatment and has not recurred.

Characteristically, a much milder form of infection was encountered in the other eight babies; in six, however, a low-grade neurological component was apparent from the changes in the CSF (Figure

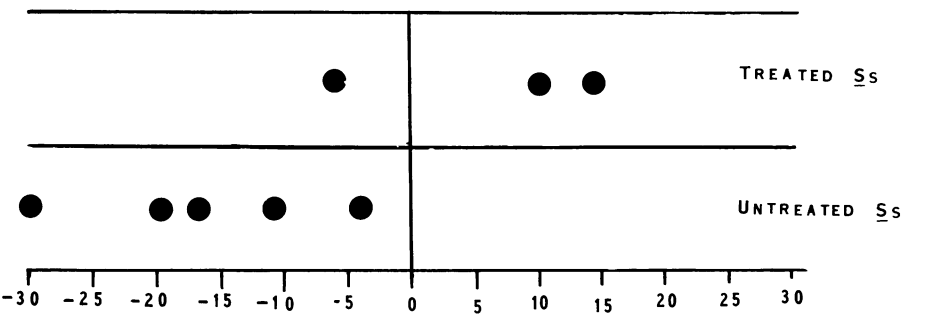


Fig. 4. Differences in I.Q. points between infected babies and their matched controls. Reproduced by permission from Saxon, S. A., Knight, W., Reynolds, D. W., Stagno, S., and Alford, C. A.: Intellectual deficits in children born with subclinical congenital toxoplasmosis: A preliminary report. *J. Pediat. 82*:792-97, 1973.

1). Persistent lymphocytosis was detected in all and elevations of CSF protein were observed in four. The elevation of protein level in this group was less marked and ranged from 150 to 285 mg./100 ml., approximately four to 10-fold less than in the two patients who proved to have severe disease (Figure 1). Follow-up data for a typical case are shown in Figure 3.[14] The CSF abnormalities in this case persisted for shorter periods and physical and mental development progressed in a relatively normal manner for the first year. There were suggestions from the longitudinal Gesell rating among a few infants with subclinical infection that fine motor and linguistic development were somewhat retarded but not enough to be impressive. No other stigmata of congenital toxoplasmosis with delayed onset, such as chorioretinitis, were observed during the follow-up period, which has ranged from two to four years.

However, when more discrete testing of intellectual and social development was done after two years, subtle but significant abnormalities in the function of the CNS were demonstrated.[20] The composite data for I.Q. development are shown in Figure 4, where the differences in I.Q. points between individual infected babies and their matched controls are depicted.[20] Although there was no difference in social quotients between any of the groups, there was significant lowering of I.Q. in the children who had untreated subclinical congenital toxoplasmosis. The average reduction compared to controls was 17 points (93 in the infected group as opposed to 110 in controls). Such

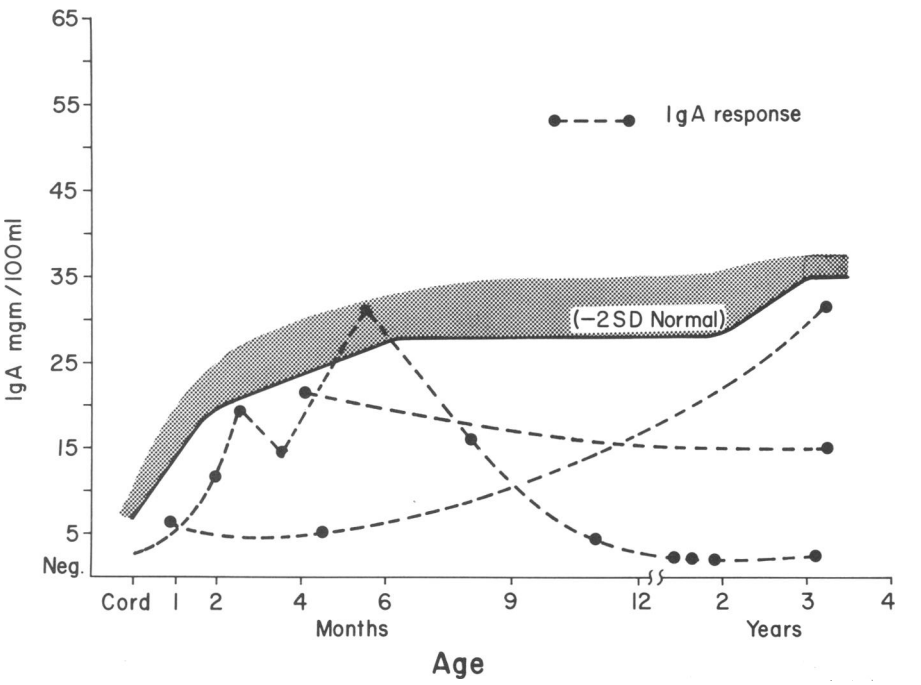


**Fig. 5. Abnormal IgA responses in congenital toxoplasmosis.**

infants will undoubtedly be slow learners and will probably encounter difficulties in school unless their intellectual abilities improve with time. Gross and fine motor control was also retarded in untreated infected babies but less than I.Q.

Interestingly, the three babies who were treated with sulfadiazine and pyrimethamine shortly after delivery and who were available for testing later had totally normal development, including I.Q. Obviously, the number of patients studied is too small to permit conclusions about the outcome of treatment in subclinical disease but the preliminary data are provocative. They suggest that early treatment of the low-grade infection, which is by far the most common form, may prove to be beneficial even though treatment of disease which is already far advanced at birth (severe disease) seems less helpful.[2] In order for this to be done, however, laboratory aids such as the IgM-FA for the early detection of subclinical infection must be developed for general use. Certainly all of our subclinical infections in infants were detectable

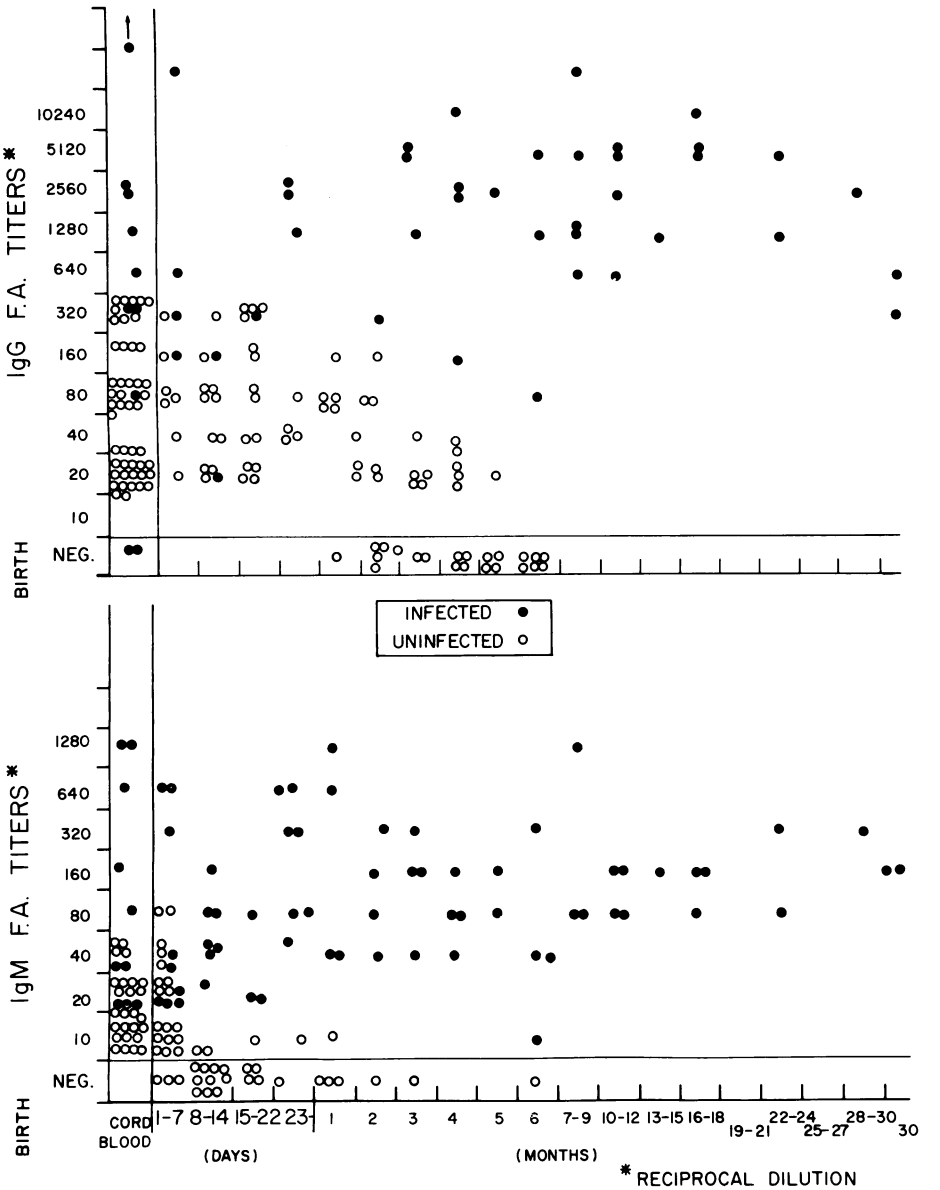


Fig. 6. Fluorescent-antibody levels in uninfected infants and those with congenital toxoplasmosis.

within a week after delivery when the IgM-FA was used as a screen and proper follow-up testing was employed to exclude false positives.

There may also be subtle abnormalities in immunoglobulin development in infants who have subclinical congenital toxoplasmosis. The data bearing on this point are shown in Figure 5. Three of the 10 infants have had retarded development of serum IgA for the first three years of life. In two, IgA levels were present but below the second standard-deviation limit of normal values as predetermined for our own population and other populations.[24,25] After a slow start, IgA disappeared entirely from the serum of the third infant after six months of age and has remained absent since then. Whether this abnormality has or will eventually result in an increased tendency to secondary infections or other immune abnormalities is not clear. In this respect congenital toxoplasmosis resembles another chronic intrauterine infection: namely, congenital rubella.[26]

Unlike IgA, IgM and IgG development seems to be excessive during the early years of life, just as in congenital rubella, cytomegalovirus disease, and syphilis.[14, 17, 26-28] Such findings suggest persistent and excessive antigenic stimulation as another component of these chronic infections, at least in some cases. The degree of increased IgM and IgG development seems to be related directly to the severity of infection but development is increased over normal in subclinically infected patients as a group.[17, 26, 28, 31] These data beg the question of whether or not immune complex disease will be another late feature of the chronic congenital infections, including the varieties that are subclinical at birth.

## Longitudinal Serological Studies

IgG and IgM-FA antibody levels as determined serially in infected infants and controls are shown in Figure 6, and serial values for individual infected infants are depicted in Figure 7. Controls for these studies were babies born with reactive IgG-FA sera who were subsequently shown to be uninfected by serial determinations performed over an interval of six to seven months.[15, 29, 30] Serial dye-dilution antibody levels were also obtained in half of the infected and control populations to show that they paralleled the IgG-FA level, as previously reported.[29, 30]

Levels of total fluorescent antibodies, which measure predominantly IgG activity, ranged in titer from 1/10 to 1/320 in cord sera collected

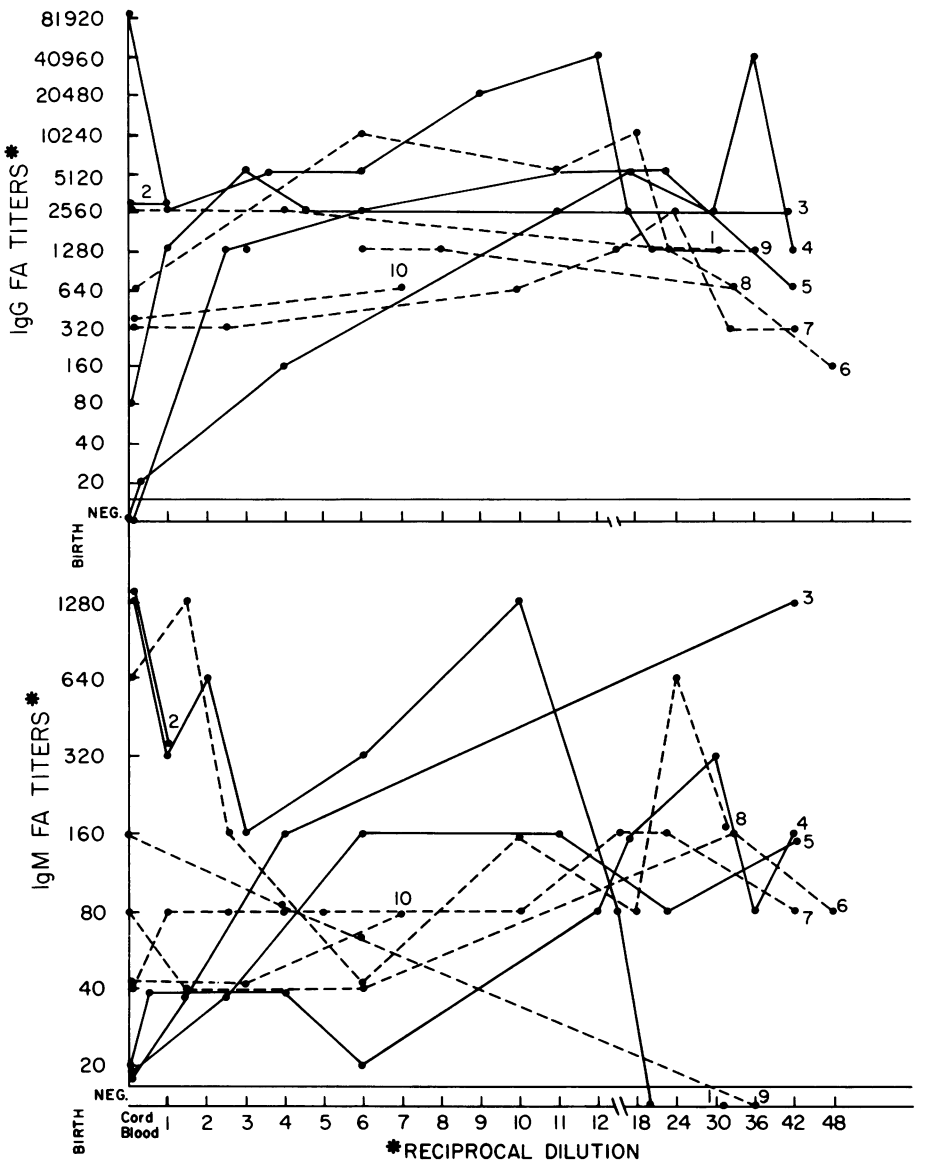


Fig. 7. Fluorescent antibody levels in individual infants with congenital toxoplasmosis.

from uninfected newborns. This transplacental maternal antibody disappeared from the sera of all in the first seven months of life, as noted in Figure 6. In infected infants, however, the range of titers in cord sera were broader, from negative to 1/81,920. But from a diagnostic standpoint, levels in cord sera obtained from infected infants overlapped those from uninfected infants in 50% of the cases. This overlap was maintained for a number of weeks after delivery. The two infected infants who had no IgG *Toxoplasma* antibody at birth are of special importance with regard to serological diagnosis since in these two cases the diagnosis would have been missed if the procedures which measure total fluorescent antibodies were used for screening. Moreover, there was no significant difference between the titers of IgG-FA antibody in the maternal sera collected at delivery and that in cord sera, whether the neonate was infected or not.

The level of IgG-FA antibody in infected infants who were born with a low level ($\leq$1/80), especially those with negative values, increased rapidly in the first six months following delivery, as noted in Figure 7. In one instance significant levels were detected as early as two weeks after delivery. Infected infants who were born with titers between 1/640 and 1/2,560 tended to maintain their relatively high levels throughout the first year of life while the titer rapidly dropped into this range in one infant who was born with an excessively high level. Levels of total fluorescent antibody in infected infants waned only slightly over the four-year observation period. This was also true with respect to maternal values. Two to three months elapsed before infected infants could be segregated on serologic findings based on the total or IgG-FA test (Figure 6). Dye-dilution antibody levels, although four to eightfold higher, paralleled the IgG-FA antibody titers during the first six months of life.

IgM-FA antibody levels in uninfected newborns ranged from 1/10 to 1/80, while those in infected infants varied from 1/20 to 1/1,280 (Figure 6). Again there was an overlap in 50% of the infected cases. In contrast to IgG antibody, this overlap was maintained for only a week after delivery as IgM-FA antibody levels of uninfected infants became negative or fell to an insignificant titer (1/10) while they remained constant or increased in infected neonates. Thus, the infected population was segregated on the basis of IgM-FA tests one week after delivery. Also, with regard to diagnosis, the two infants who were

born without demonstrable IgG antibody had significant though low levels of IgM-FA antibody in their cord sera.

The pattern of IgM antibody development during the first year in infected infants paralleled the development of IgG antibody. Levels of IgM antibody rose during the first six months if they were low initially, remained constant if they had been in the intermediate range at birth, and fell if they had been very high originally. Except in two patients in whom IgM antibodies disappeared after the first year, levels remained approximately constant between 1/80 and 1/320 during the remaining three years of observation (Figure 7).

Treatment of neonates with sulfadiazine and pyrimethamine had no significant effect on either IgG or IgM antibody development as measured by the FA tests.

If IgM antibody detection is to be used as a screening technique for congenital infection with toxoplasmosis, it must be done as soon as possible after delivery since in the majority of infants, even those subclinically involved, IgM-antibody production is persistent. This has been observed previously by Remington.[32] Persistence of this antibody type, which has a short half life, makes prolonged production of antigen probable in both congenital and postnatally-acquired toxoplasmosis. Whether the antigen is produced by viable encysted organisms or is derived from persistent or intermittent circulation of the proliferative forms of *Toxoplasma* is not clear. But its prolonged production in the presence of persistent specific antibody lends further credence to the concept that the formation of immune complexes and the attendant vascular damage might lead eventually to dysfunction in crucial organs, such as the kidney. Should this prove true, low-grade and long-term damage need not be related exclusively to invasion of cells by the proliferative form of *Toxoplasma.*

The presence of low levels of IgM-*Toxoplasma* antibody in the apparent absence of IgG antibody at birth in two of our infected infants was surprising, especially in view of the small number of patients studied. It might have been expected that any IgG antibody produced by the mother would be transferred to the fetus, especially in late gestation, when mechanisms of placental transfer are mature.[17, 28, 33] In fact, given enough time, the infected fetus should have produced IgG antibody when lacking the feedback inhibition of maternal IgG antibody.[17, 34] Thus, the serological response in these cases suggests

that the mother may have acquired and transferred infection very late in gestation, a factor that could well have influenced outcome in favor of relative avirulence. Unfortunately, maternal sera collected at or near the time of delivery were not available for testing in the two cases under discussion; hence this suggestion must remain speculative. Clearly, however, screening newborns with tests that detect predominately IgG antibody, such as the standard FA procedure, will not detect all cases of congenital infection, even if the necessary follow-up sera are examined. Perhaps the dye-dilution tests would be superior for this purpose.

It would be remiss not to mention the definite technical difficulties encountered when the IgM-FA is used as a screening procedure; these have not been as important as when suspect cases are being corroborated. The most serious problem, the cause of which is unknown, is the total lack of reactivity of many batches of commercially available conjugated antihuman IgM antibody. In fact, only a few of the many tested were reactive and these reacted to a variable degree against the same known positive sera (originally they were standardized against Remington's conjugate). There is essentially no ready supply of commercial antihuman IgM antisera available that could be used for screening the general population of newborns with the IgM-FA test, to say nothing about standardization of those that are reactive. False-positive reactions also occur, seemingly because of contaminating anti-IgG components which are not detectable in the usual precipitin procedures used to show specificity of the anti-IgM antisera. The latter is a less serious problem for screening than the former; both need improvement before screening can be done on a large scale. For this purpose, readily available and *standardized* materials (antigen, control sera, and conjugated antisera) will be essential.[32]

## Treatment of Congenital Toxoplasmosis

Present-day treatment of *Toxoplasma* infections of any sort in man is based on earlier studies of therapeutic trials in the rat and on sporadic treatment of different types in too few cases of infection in man.[35-39] No controlled clinical trials have been attempted in humans. For many reasons too numerous to cite here this would be almost impossible to do at present. Discussion of problems may be found in any standard text on medical therapy.[40, 41] In spite of these glaring deficiencies, it is

generally felt that the sequelae of toxoplasmosis, at least of the brain and eye, are so dangerously acute or so debilitating in the long run as to make treatment justifiable, even if we are unsure of its efficacy.[42]

The proliferative form of the *Toxoplasma* can clearly be inhibited by drugs or by combinations of drugs which interfere with folic-acid metabolism; some strains are quite sensitive in this regard.[38, 41] Pyrimethamine (Daraprim), sulfonamides, and combinations of these have been investigated most extensively in both animals and man, and combined therapy with these drugs has emerged as the generally preferred form of treatment.[40-42] A new drug, Spiramycin, is being used extensively in Europe but remains an experimental compound in the United States. Anecdotal reports from Europe suggest that Spiramycin might be the preferred therapy. It is being tried in the treatment of *Toxoplasma* infections in pregnancy, as pyrimethamine and sulfadiazine have been. However, American workers justifiably believe that any treatment which is given during pregnancy and is directed at control of fetal infection is premature until efficacy and lack of toxicity to the mother and to the fetus can be shown conclusively. Up to the present time, such data have not been sufficiently convincing to justify any kind of treatment in pregnant women except that directed at saving the life of the mother, who is seldom in jeopardy.

Congenital infection, especially if symptomatic in the young infant, is dangerous enough to warrant treatment. Usually it is given as follows:[40-42]

*Pyrimethamine.* 1 mg./kg. of body weight per 24 hours given orally in equal doses at intervals of 12 hours, the maximal dose being 25 mg. per day. The *Physician's Desk Reference* advocates reducing the dose by one half (0.5 mg./kg./24 hr.) after four days in infants and children and maintaining this level during the one-month treatment period. This is the regimen that we employed in our subclinically infected infants. Others have recommended that the initial dose may be doubled (2 mg./kg./24 hr.) for two days and continued at 1 mg./kg./24 hr. for one month. The higher dosage schedules should probably be employed if the infant is ill. The theory here is to reduce the number of circulating proliferative forms of *Toxoplasma* as soon as possible without producing undue acute toxicity, in order to minimize continuing tissue damage. Toxicity is itself related to dosage; it manifests primarily as bone-marrow depression involving all cellular

types. Complete blood counts and platelet counts should be obtained at least two times weekly to monitor for this effect and the maximum daily dose should be gauged on these findings. Pyrimethamine comes in 25-mg. tablets, which must therefore, be divided properly by a pharmacist for use in infants; if dosages are relatively large, vomiting may ensue. The latter can usually be relieved by reducing the dose or by giving the drug with meals. Because of the difficulties involved in administering pyrimethamine daily to young infants, especially if they are ill, an intravenous preparation has been developed. The dosage schedule of the intravenous preparation is thought to be about the same as with oral doses.[41] Clearly, with all these problems and a need for daily assessment, pyrimethamine should be administered to young infants only in a hospital, unless this is impossible to arrange.

### Sulfonamides

The efficacy of sulfadiazine was originally tested against the proliferative stage of *Toxoplasma* in animals and is the preparation that has been used most often in published reports in man. Sulfapyrazine, sulfamethazine, and sulfamerazine have similar orders of activity in animals, but other sulfonamide preparations are ineffective unless given in toxic doses.[35, 36] It appears logical, however, to use multiple sulfonamides for treatment of toxoplasmosis, because additive effect and reduced toxicity would be expected. The usual doses are 100-150 mg./kg./24 hr., with the drug being given orally in four equally divided doses per day. Along with pyrimethamine, the sulfonamide should be continued for one month. Again, the length of treatment is purely arbitrary and may have to be shortened if toxicity becomes a real problem or lengthened if the activity of the disease does not subside adequately. In our studies we used sulfadiazine at 150 mg./kg./24 hr. for one month without toxicity.

### Folinic Acid and Yeast[40-42]

Folinic acid (leucovorin-calcium) reduces the toxicity of pyrimethamine in the human by competitive inhibition but does not significantly reduce its inhibitory effect on *Toxoplasma*. Therefore, it is given (1 mg./kg./24 hr. in one dose) in order to minimize toxicity. With our schedules including this dose of folinic acid, there was no significant toxicity in 10 infants treated up to the present time. Yeast

is also advocated to reduce toxicity, but we found it difficult to administer the other three drugs properly and to give yeast to small infants; the mechanical difficulties are too great.

Evidence has been presented in this report that involvement of the central nervous system occurs in a significant proportion of newborn children with subclinical or inapparent congenital toxoplasmosis. Preliminary data on the possible efficacy of treatment in long-term outcome have been given. We believe that treatment should be instituted in any baby with proven congenital toxoplasmosis in whom changes in the cerebrospinal fluid have been demonstrated. In our limited experience, drug toxicity has not been a problem but treatment of infected newborn children should be undertaken with caution. Frequent monitoring is essential.

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